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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/513,888	02/25/00	CROCE	C	9855-30U1

000570 HM12/0425
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ONE COMMERCE SQUARE
2005 MARKET STREET, SUITE 2200
PHILADELPHIA PA 19103

EXAMINER	
LOEB, B	
ART UNIT	**PAPER NUMBER**
1636	12

DATE MAILED: 04/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/513,888	CROCE ET AL.	
	Examiner	Art Unit	
	Bronwen M. Loeb	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *27, 30, 34-36, 41-43, 45, 47-58, 63-66, 68, 73-75, 84, 86, 87, 92 and 93* is/are withdrawn from consideration.

5)☒ Claim(s) *23 and 24* is/are allowed.

6)☒ Claim(s) *1-18,20-22,25,67,90, 91, 94-97* is/are rejected.

7)☒ Claim(s) *19* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/25/00* is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8 & 9* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Continuation of Disposition of Claims: Claims pending in the application are Claims 1-25, 27, 30, 34-36, 41-43, 45, 47-58, 63-58, 73-75, 84, 86, 87 and 90-97.

DETAILED ACTION

This action is in response to the Response to Restriction Requirement dated March 23, 2001. Claims 1-25, 27, 30, 34-36, 41-43, 45, 47-58, 63-58, 73-75, 84, 86, 87 and 90-97 are pending.

Election/Restrictions

1. Applicant's election with traverse of Group I in Paper No. 11 is acknowledged. The traversal is on the ground(s) that the nucleic acids of Group I and the polypeptides of Group III represent a unitary biological entity, that the literature regarding these nucleic acids and proteins should be substantially co-extensive and that the combination search would not be a burden. This is not found persuasive because a combination search of these two different inventions are not co-extensive. For instance, one may find art on a purified protein, identified by its function or activity. Such art would not be art for the nucleic acid sequences. As stated in the Action mailed on October 23, 2000, the inventions of Groups I and III are distinct from each other because they have different chemical, biological, structural and functional distinctness. Burden was established based on their different classifications, and their art-recognized divergent subject matter.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 27, 30, 34-36, 41-43, 45, 47-58, 63-66, 68, 73-75, 84, 86, 87, 92 and 93 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

4. Claim 67 has been examined wherein the "reagent for assessing expression of FEZ1 in a cell" is a polynucleotide.

Sequence Compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply *fully* with the requirements of 37 CFR 1.821 through 1.825 because sequences were set forth that lack sequence identifiers, and it is unknown if the filed CRF and paper sequence listing contains these four sequences. These sequences include **the sequences in Figure 3B and the four nucleic acid sequences on p. 29, lines 15-16**. If the Sequence Listing required for the instant application is identical to that of another application, a letter may be submitted requesting transfer of the previously filed sequence information to the instant application. For a sample letter requesting transfer of sequence information, refer to MPEP § 2422.05. Additionally, it is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP § 2422.02).

6. Applicants are required to comply with all of the requirements of 37 CFR 1.821 through 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. 1.821 through 1.825 did not preclude the continued examination of the application on the merits, the results of which are communicated below.

Priority

7. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119 as follows:

> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

Upon review of the specifications of the parent application and comparison with the specification of the present application, it is determined that the specification of parent application 60/121,537 is not enabling for the preparation of the invention claimed in claims 91 and 97. The specification of this parent application does not teach SEQ ID No. 60 (a specific adenovirus vector), nor does it teach an isolated polynucleotide wherein the portion is substantially homologous with at least 50 consecutive nucleotide residues of a strand of a human FEZ1 gene. Since these recitations are not disclosed in the parent application and cannot be predicted from the teachings of the parent application, the parent application is not enabling for the presently claimed invention. Thus, the requirements of the first paragraph of 35 U.S.C. 112 have not been complied with. Accordingly, claims 91 and 97 are assigned an effective filing date of February 25, 2000.

Drawings

8. The drawings are objected to because in Figure 23, "minutes" is misspelled and the y-axis lacks a legend. Correction is required.

Specification

9. The disclosure is objected to because of the following informalities: the specification refers to a Figure 5 but no Figure 5 is present. This drawing is deemed not necessary to understanding the claimed invention. Therefore, its absence does not render the application incomplete. A complete response to this action must include a copy of Figure 5, as supported by the Brief Description of the Drawings on pp. 17-18. See 35 U.S.C. § 113, 37 C.F.R. § 1.81 and MPEP § 608.02 "Drawing Requirements".

On p. 17, line 17, it is stated that the sequence in Figure 4B is SEQ ID No. 6, however, it appears to be SEQ ID No. 5. On p. 15, lines 4 and p. 96, lines 17, a protein is labeled "KIAA0522" however in the sequence listing for SEQ ID No. 8, it is listed as "KIA0522". Figure 9 appears to be the results of the experiment on p. 107, lines 11-19; if correct, Figure 9 should be referred to in this section. On p. 106, line 15 there is the phrase "dead cells were excluded the dead cells by" which is confusing.

Appropriate correction is required.

Claim Objections

10. Claim 19 is objected to because of the following informalities: it recites the phrase "polynucleotides are linked by non-naturally occurring linkage other than a phosphodiester linkage". A phosphodiester linkage is not a non-natural linkage in polynucleotides. Appropriate correction is required.

11. Applicant is also advised that should claim 4 be found allowable, claim 94 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 67 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of

the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claim is broad. Claim 67 encompasses a kit for selecting any anti-cancer therapeutic compound for administration to a human afflicted with any cancer.

The nature of the invention is kit comprising an isolated polynucleotide reagent for assessing expression of FEZ1 in a cell and a plurality of candidate anti-cancer therapeutic compounds. The claim is essentially directed to a method for selecting an anti-cancer therapeutic compound for any cancer.

An analysis of the prior art as of the effective filing date of the present application shows a loss of heterozygosity (LOH) in band 21-22 of human chromosome 8 in a wide range of different cancers. See, for instance, Boige et al (1997 Cancer Research 57: 1986-1990); El-Naggar et l (1998 Oncogene 16: 2983-2987); and Anbazhagan et al (1998 Am. J. Pathology 152: 815-819). Putative tumor suppressor genes have been identified in this chromosomal region; their role has not been definitively established. The prior art further suggests that a wide range of LOH's may be associated with a particular disease, which may correlate to the genetic complexity underlying these cancers. See Kerangueven et al (1997 Cancer Research 57: 5469-5474). As additional evidence of the complexity of cancer, and the unpredictable nature regarding its cause and progression, chromosome 8 complementation in different colorectal cancer cell lines has different responses, indicating the role of unknown other genetic

mutations in these various cell lines. See Gustafson et al (1996 Cancer Research 56: 5238-5245). No prior art teaches definitive evidence of the role of expression of the FEZ1 gene and any cancer.

The relative skill of those in the art of cancer and cancer therapeutics is high.

The area of the invention is unpredictable. The fundamental mechanism of disease has been determined for very few cancers, therefore one is unable to model what specific types of compounds will be therapeutic for any particular cancer. Since the role of FEZ1 expression has not been established in any cancer, there is no factual basis on which to model predictions about the therapeutic nature of compounds. In a given cancer type, there can be a wide range of diversity in the genetic basis of the disorder, rendering accurate prediction even less possible. Therefore, there is little more than extensive trial and error available to assess which compounds among those that affect expression of the FEZ1 gene are likely to be therapeutic for the wide range of cancers disclosed.

The present specification provides little direction of guidance to support the claimed invention. The specification generally discloses the use of the kit for a very broad group of cancers, and disorders including tubulin hyperpolymerization disorders and tubulin hypopolymerization disorders. The specification discloses a correlation between FEZ1 expression and some different primary tumors, or cell lines. The specification does not disclose the statistical significance of the data, or establish whether FEZ1 expression is a causal factor in any particular cancer. Methods of assessing the effect of a compound on the expression of a gene are well known in the

art. However, the specification provides no direction as to how to predict which compounds among those that affect expression of the FEZ1 gene are likely to be therapeutic.

No working examples are disclosed which are encompassed by the claim.

The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed kit. In order to determine how to use the claimed kit for selecting an anti-cancer therapeutic compound, one of skill in the art would have to determine if FEZ1 expression was fundamentally related to the disease mechanism for any given disease, and then would have to determine the therapeutic capacity of any compound shown to affect FEZ1 expression. Since neither the prior art nor the specification provides the answers to these questions, one of skill in the art would have to undertake a large quantity of trial and error experimentation to answer them.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the claimed kit for selecting an anti-cancer therapeutic compound for administration to a human afflicted with a cancer.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 2, 7, 14, 16, 20-22, 25, 91, 95 and 97 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 7, 14, 18, 22, 25, 91, and 95 recite either "has" or "having" which render the claims vague and indefinite. "Has" or "having" are not legally defined terms so it is unclear whether they are open or closed. It is suggested that the claims be amended to recite "comprising" or "consisting of" as is appropriate.

Claim 16 recites "an immobilized polynucleotide" as a member of the Markush group of "detectably labeled isolated polynucleotide". It is unclear how an immobilization is a detectable label.

Claim 18 recites the phrase "substantially purified" which renders the claim vague and indefinite. The specification does not specify an actual minimum.

Claim 20 recites "and combinations of such linkages" at the end of a Markush group from which a non-naturally occurring linkage is selected. It is unclear how a single linkage could be a combination of the recited linkages.

Claim 21 recites "an end of the isolated polynucleotide is nucleolytically blocked" which is vague and indefinite. Is the blocked end achieved nucleolytically or is the end blocked against nucleolytic agents?

Claim 97 is vague and indefinite because it is unclear what the phrase "the portion is substantially with at least 50 consecutive nucleotide residues". Did Applicant intend to recite "substantially homologous"?

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

17. Claims 1-5, 12-16, 18 and 94-97 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsubara et al (EP 0679716 A1 and Database Geneseq, Accession number T23583). Matsubara et al teach an isolated polynucleotide of at least 50 consecutive nucleotide residues that are completely homologous to a strand of SEQ ID No. 1. The isolated nucleic acid sequence is in a nucleic acid vector. The sequence is detectably labeled with ^{32}P in the course of sequencing or for use as a probe. Immobilizing the isolated nucleic acid by affixing it to an affinity chromatographic resin is suggested, for selecting genes out of cDNA libraries. Isolated nucleic acids which are substantially purified are taught, such as PCR products purified from low-melting agarose gel and human genomic DNA which is restriction-enzyme digested and separated for Southern blots. See pp.1-20, especially pp. 6, 7, 15 and 16.

18. Claims 1-5, 8-14, 90 and 94-96 are rejected under 35 U.S.C. 102(e) as being anticipated by Humphries (USP 5,804,177). Humphries teaches an isolated polynucleotide (SEQ ID No. 1) which comprises at least thirty consecutive nucleotides

completely homologous to a strand of SEQ ID No. 1 in the instant application. The isolated polynucleotide further comprising a promoter is taught. The polynucleotide is in a nucleic acid vector and the vector may be an adenovirus vector. See Fig. 1, SEQ ID No. 1, col. 6, lines 26-31, and col. 7, lines 39-58.

19. Claims 1, 2, 4, 5, 12-16 and 94-96 are rejected under 35 U.S.C. 102(e) as being anticipated by Chader et al (USP 5,840,686). Chader et al teaches an isolated polynucleotide (SEQ ID No. 11) which comprises at least twenty consecutive nucleotides completely homologous to a strand of SEQ ID. No. 1. The isolated polynucleotide was cloned into a nucleic acid vector (PT7 Blue vector). The isolated polynucleotide was detectably labeled using either fluorescence label for fluorescence sequencing. See SEQ ID No. 11, col. 2, lines 41-43, col. 18, lines 64-67, col. 19, line 1-col. 20, line 29.

20. Claims 1-5, 14 and 94-96 rejected under 35 U.S.C. 102(a) as being anticipated by Database GenEmbl, Accession No. G43056 (and the associated publication: Wang et al (1998) Science 280:1077-1082). The disclosed polynucleotide sequence comprises at least 50 consecutive nucleotide residues that are completely homologous to a strand of SEQ ID NO. 1.

21. Claim 97 is rejected under 35 U.S.C. 102(b) as being anticipated by Database GenEmbl, Accession No. G43056 (and the associated publication: Wang et al (1998) Science 280:1077-1082). The disclosed polynucleotide sequence comprises at least 50 consecutive nucleotide residues that are completely homologous to a strand of SEQ ID NO. 1.

22. Claims 1-5, 14 and 94-97 are rejected under 35 U.S.C. 102(b) as being anticipated by Database EST, Accession no. N21184. The disclosed polynucleotide sequence comprises at least 50 consecutive nucleotide residues that are completely homologous to SEQ ID No. 1.

23. Claims 1-7, 14, 22 and 94-96 are rejected under 35 U.S.C. 102(a) as being anticipated by Database EST, Accession no. AI042490. The disclosed polynucleotide sequence comprises at least 50 consecutive nucleotide residues that are completely homologous to SEQ ID No. 1 and to SEQ ID No. 3. The disclosed polynucleotide is substantially homologous to at least 20 consecutive nucleotide residues in the region of nucleotide residues 1701-2510

24. Claim 97 is rejected under 35 U.S.C. 102(b) as being anticipated by Database EST, Accession no. AI042490. The disclosed polynucleotide sequence comprises at least 50 consecutive nucleotide residues that are completely homologous to SEQ ID No. 1.

25. Claim 97 is rejected under 35 U.S.C. 102(a) as being anticipated by Ischii et al (1999 PNAS 96:3928-3922 and associated GenBank Accession no. AF123654). Ischii et al teach an isolated polynucleotide sequence (FEZ1 gene) that comprises at least 50 consecutive nucleotide residues that are completely homologous to SEQ ID No. 1.

Claim Rejections - 35 USC § 103

26. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

27. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

28. Claims 1-5, 14, 17 and 94-97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Database EST, Accession no. N21184 as applied to claims 1-5, 14 and 94-97 above, and in view of Lockhart et al (1996 Nature Biotechnology 14: 1675-1680). Accession no. N21184 discloses a polynucleotide that is an expressed sequence is germ cell tumors. Lockhart et al teach gene chips comprising high-density oligonucleotide arrays for use with sequences from the human genome. At the time the invention was made, it would have been obvious to one of ordinary skill in the art to use the isolated polynucleotide from Accession no. N21184 in the gene chip array of Lockhart et al. One would have been motivated to do so in order to study the expression and regulation, for instance, of the sequence which is of interest as it is expressed in germ cell tumors, and because Lockhart et al describe the advantage of

their gene chip array for use with EST sequences. See Lockhart et al p. 1679, first column, first full paragraph.

Conclusion

Claim 19 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 23 and 24 are allowed. Claims 1-18, 20-22, 25, 67, 90, 91 and 94-97 are rejected. Claims 20, 21, 25, 67 and 91 are free of prior art.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 9:30 AM to 6:00 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Richard Schwartz, can be reached on (703) 308-1133.

Any inquiry of a general nature or relating to the status of this application should be directed to Dianiece Jacobs, Patent Analyst whose telephone number is (703) 305-3388.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

April 20, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER